(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 758 895 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
26.01.2000 Bulletin 2000/04

(21) Application number: **95916467.4**

(22) Date of filing: **21.04.1995**

(51) Int. Cl.[7]: **A61K 31/485**

(86) International application number:
PCT/US95/04897

(87) International publication number:
WO 95/28930 (02.11.1995 Gazette 1995/47)

(54) SUBLINGUAL DOSAGE FORMS CONTAINING APOMORPHINE FOR USE IN THE TREATMENT OF ERECTILE DYSFUNCTION

SUBLINGUALE DOSIERUNGSFORMEN ENTHALTEND APOMORPHIN ZUR VERWENDUNG BEI DER BEHANDLUNG VON EREKTILER DYSFUNKTION

FORMES GALENIQUES SUBLINGUALES CONTENANT DE L'APOMORPHINE POUR L'UTILISATION DANS LE TRAITEMENT DU DYSFONCTIONNEMENT ERECTILE

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

(30) Priority: **22.04.1994 US 231250**

(43) Date of publication of application:
26.02.1997 Bulletin 1997/09

(60) Divisional application:
99121684.7

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(56) References cited:
EP-A- 0 579 435 **WO-A-94/22445**
US-A- 4 727 064

- **BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, Volume 26, Issued 1988, P. DANJOU et al., "Assessment of Erectogenic Properties of Apomorphine and Yohimbine in Man", pages 733-739.**
- **JOURNAL OF UROLOGY, Volume 145, issued June 1991, R. SEGRAVES et al., "Effect of Apomorphine on Penile Tumescence in Men with Psychogenic Impotence", page 1175.**
- **PROGRESS OF NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY, Volume 12, Issued 1988, S. LAL, "Apomorphine in the Evaluation of Dopaminergic Function in Man", pages 117-164.**
- **GOODMAN &GILMAN'S, THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 9th EDITION, page 72**
- **GOODMAN &GILMAN'S, THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 8th EDITION, page 57**
- **MARTINDALE, THE EXTRA PHARMACOPOEIA, 28th EDITION, 1982, PAGES 891-892**

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

Printed by Xerox (UK) Business Services
2.16.7/3.6

EP 0 758 895 B1

Description

[0001] This invention relates to the use of apomorphine-containing compositions for amelioration of erectile dysfunction in male patients and for diagnostic purposes.

[0002] A normal erection occurs as a result of a coordinated vascular event in the penis. This is usually triggered neurally and consists of vasodilation and smooth muscle relaxation in the penis and its supplying arterial vessels. Arterial inflow causes enlargement of the substance of the corpora cavernosa. Venous outflow is trapped by this enlargement, permitting sustained high blood pressures in the penis sufficient to cause rigidity. Muscles in the perineum also assist in creating and maintaining penile rigidity. Erection may be induced centrally in the nervous system by sexual thoughts or fantasy, and is usually reinforced locally by reflex mechanisms. Erectile mechanics are substantially similar in the female for the clitoris.

[0003] Impotence or male erectile dysfunction is defined as the inability to achieve and sustain an erection sufficient for intercourse. Impotence in any given case can result from psychological disturbances (psychogenic), from physiological abnormalities in general (organic), from neurological disturbances (neurogenic), hormonal deficiencies (endocrine) or from a combination of the foregoing.

[0004] These descriptions are not exact, however. There is currently no standardized method of diagnosis or treatment. As used herein, psychogenic impotence is defined as functional impotence with no apparent overwhelming organic basis. It may be characterized by an ability to have an erection in response to some stimuli (e.g., masturbation, spontaneous nocturnal, spontaneous early morning, video erotica, etc.) but not others (e.g., partner or spousal attention).

[0005] Various methods for the treatment of impotence have been suggested, including external devices, for example, tourniquets (see U.S. Patent No. 2,818,855). In addition, penile implants, such as hinged or solid rods and inflatable, spring driven or hydraulic models, have been used for some time. The administration of erection effecting and enhancing drugs is taught in U.S. Patent No. 4,127,118 to LaTorre. That patent teaches a method of treating male impotence by injecting into the penis an appropriate vasodilator, in particular, an adrenergic blocking agent or a smooth muscle relaxant to effect and enhance an erection. More recently, U.S. Patent No. 4,801,587 to Voss et al. teaches the application of an ointment to relieve impotence. The ointment consists of the vasodilators papaverine, hydralazine, sodium nitroprusside, phenoxybenzamine, or phentolamine and a carrier to assist absorption of the primary agent through the skin. U.S. Patent No. 5,256,652 to El-Rashidy teaches the use of an aqueous topical composition of a vasodilator such as papaverine together with hydroxypropyl-β-cyclodextrin.

[0006] Recently the effect of apomorphine on penile tumescence in male patients afflicted with psychogenic impotence has been studied. These studies show that while apomorphine can indeed induce an erection in a psychogenic male patient, the apomorphine dose required to achieve a significant erectile response is usually accompanied by nausea or other serious undesirable side effects such as hypertension, flushing and diaphoresis. The specific mechanisms by which apomorphine acts to produce an erectile response in a human patient are not yet completely understood, however.

[0007] Moreover, apomorphine has been shown to have very poor oral bioavailability; see, for example, Baldessarini et al., in Gessa et al., eds., Apomorphine and Other Dopaminomimetics, Basic Pharmacology, Vol. 1, Raven Press, N.Y. (1981), pp. 219-228, and Goodman & Gilman's The Pharmacological Basis of Therapeutics, 8 th. Edition, 1990, p. 57.

[0008] Thus the search is continuing for an effective treatment of functional impotence in male patients as well as for diagnostic methods that can identify such patients. It has now been found that sublingual delivery systems for apomorphine can provide a practical therapeutic and/or diagnostic "window" while reducing the likelihood of undesirable side effects. Thus, the present invention relates to the subject matter as defined in claim 1. Claims 2 to 11 relate to preferred embodiments.

[0009] It has been found that, for an optimal erectile response, steady state circulating serum and mid-brain tissue levels of apomorphine are to be maintained within a relatively closely defined range.

[0010] Sublingual apomorphine dosage forms, usually containing about 2.5 to about 10 milligrams of apomorphine, and dissolving in water within a time period of at least about 2 minutes but less than about 10 minutes, preferably about 3 minutes to about 5 minutes, have been found to be effective in male patients suffering from psychogenic erectile dysfunction for the induction and maintenance of an erection sufficient for intercourse (i.e., vaginal penetration) without nausea or other undesirable side effects. The apomorphine is administered sublingually, preferably about 15 to about 20 minutes prior to sexual activity, and so as to maintain a predetermined circulating serum levels and mid-brain tissue levels of apomorphine during the period of sexual activity.

[0011] The foregoing sublingual apomorphine dosage farms are also suitable for screening patients complaining of erectile dysfunction so as to identify patients of psychogenic etiology.

[0012] In the drawings

FIGURE 1 is a graphical representation of mean erectile function, expressed as RIGISCAN™ monitor value, as a

function of apomorphine dose;

FIGURE 2 is a bar graph depicting the percent successful erectile function for placebo, 3-milligram apomorphine dose, and 4-milligram apomorphine dose under erotic and neutral conditions; and

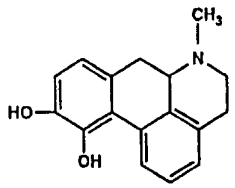
FIGURE 3 is a bar graph presenting yet another comparison of erectile function noted in Pilot study #4 in terms of RIGISCAN™ monitor score versus placebo, 3 milligrams of apomorphine and 4 milligrams of apomorphine under erotic and neutral conditions.

[0013] Apomorphine is a dopamine receptor agonist that has a recognized use as an emetic when administered subcutaneously in about a 5-milligram dose. For the purposes of the present invention, apomorphine or a similarly acting dopamine receptor agonist is administered in an amount sufficient to excite cells in the mid-brain region of the patient but with minimal side effects. This cell excitation is believed to be part of a cascade of stimulation that is likely to include neurotransmission with serotonin and oxytocin.

[0014] The dopamine receptors in the mid-brain region of a patient can be stimulated to a degree sufficient to cause an erection by the sublingual administration of apomorphine over a time period in the range of about 2 to about 10 minutes. The amount of apomorphine administered sublingually over this time period preferably is in the range of about 25 micrograms per kilogram (μg/kg) of body weight to about 60 μg/kg of body weight.

[0015] The apomorphine is administered preferably about 15 to about 20 minutes prior to sexual activity.

[0016] Apomorphine can be represented by the formula



and exists in a free base form or as an acid addition salt. For the purposes of the present invention apomorphine hydrochloride is preferred; however, other pharmacologically acceptable moieties thereof can be utilized as well. The term "apomorphine" as used herein includes the free base form of this compound as well as the pharmacologically acceptable acid addition salts thereof. In addition to the hydrochloride salt, other acceptable acid addition salts are the hydrobromide, the hydroiodide, the bisulfate, the phosphate, the acid phosphate, the lactate, the citrate, the tartarate, the salicylate, the succinate, the maleate, the gluconate, and the like.

[0017] Illustrative preferred sublingual dosage forms are set forth in Table I, below.

TABLE I

150-Milligram Apomorphine Hydrochloride Sublingual Tablets	
3-mg Tablet	
Apomorphine Hydrochloride	2.00 wt-%
Mannitol	66.67 wt-%
Ascorbic Acid	3.33 wt-%
Citric Acid	2.00 wt-%
Avicel PH102	15.00 wt-%
Methocel E4M	10.00 wt-%
Aspartame	0.67 wt-%
Magnesium Stearate	0.33 wt-%
4-mg Tablet	
Apomorphine Hydrochloride	2.66 wt-%
Mannitol	66.00 wt-%
Ascorbic Acid	3.33 wt-%
Citric Acid	2.00 wt-%
Avicel PH102	15.00 wt-%
Methocel E4M	10.00 wt-%
Aspartame	0.67 wt-%
Magnesium Stearate	0.33 wt-%
5-mg Tablet	
Apomorphine Hydrochloride	3.33 wt-%
Mannitol	65.34 wt-%
Ascorbic Acid	3.33 wt-%
Citric Acid	2.00 wt-%
Avicel PH102	15.00 wt-%
Methocel E4M	10.00 wt-%
Aspartame	0.67 wt-%
Magnesium Stearate	0.33 wt-%

[0018] If desired, and in order to facilitate absorption and thus bioavailability, the presently contemplated dosage forms can also contain, in addition to tabletting excipients, β-cyclodextrin or a β-cyclodextrin derivative such as hydroxypropyl-β-cyclodextrin (HPBCD). Illustrative dosage forms containing HPBCD are shown in Tables II and III, below.

TABLE II

Apomorphine Hydrochloride Sublingual Tablets With Hydroxypropyl-β-Cyclodextrin	
	mg/Tab
Apomorphine Hydrochloride	4.0

TABLE II (continued)

Apomorphine Hydrochloride Sublingual Tablets With Hydroxypropyl-β-Cyclodextrin	
	mg/Tab
HPBCD	5.0
Ascorbic Acid	10.0
PEG8000	39.5
Mannitol	39.5
Aspartame	2.0
TOTAL	100.0

TABLE III

Apomorphine Hydrochloride Sublingual Tablets With β-Cyclodextrin	
	mg/Tab
Apomorphine Hydrochloride	5.0
β-Cyclodextrin	20.0
Ascorbic Acid	5.0
Mannitol	68.9
Magnesium Stearate	1.0
D&C Yellow 10 Aluminum Lake	0.1
TOTAL	100.0

[0019] The onset of nausea can be obviated or delayed by delivering apomorphine at a controlled dissolution rate so as to provide circulating serum levels and mid-brain tissue levels of apomorphine sufficient for an erection without inducing nausea. When apomorphine is administered at or near the relatively higher amounts of the aforementioned dosage range, the likelihood of nausea onset can be reduced by concurrent administration of a ganglionic agent (inhibitor of ganglionic response) such as nicotine or lobeline sulfate. For this purpose, the weight ratio of apomorphine to ganglionic agent is in the range of about 10 to about 1.

[0020] Other antiemetic agents that can be used in conjunction with apomorphine are antidopaminergic agents such as metoclopramide, and the phenothiazines, e.g., chlorpromazine, prochlorperazine, pipamazine, thiethylperazine, oxypendyl hydrochloride, and the like. Also suitable are the serotonin (5-hydroxytryptamine or 5-HT) antagonists such as domperidone, odansetron (commercially available as the hydrochloride salt under the designation Zofran®), and the like, the histamine antagonists such as buclizine hydrochloride, cyclizine hydrochloride, dimenhydrinate (Dramamine), and the like, the parasympathetic depressants such as scopolamine, and the like, as well as other anti-emetics such as metopimazine, trimethobenzamide, benzquinamine hydrochloride, diphenidol hydrochloride, and the like.

[0021] Nicotine-containing dosage forms and domperidone-containing dosage forms are illustrated in Table IV, below.

TABLE IV

Apomorphine Hydrochloride Sublingual Tablets Containing an Anti-Emetic Agent	
	mg/Tab
Apomorphine Hydrochloride	5.0
Ascorbic Acid	5.0
Mannitol	67.9
Magnesium Stearate	1.0
Nicotine	1.0
β-Cyclodextrin	20.0
D&C Yellow 10 Aluminum Lake	0.1
TOTAL	100.0
	mg/Tab
Apomorphine Hydrochloride	5.0
Ascorbic Acid	5.0
Mannitol	58.9
Magnesium Stearate	1.0
Domperidone	10.0
β-Cyclodextrin	20.0
D&C Yellow 10 Aluminum Lake	0.1
TOTAL	100.0

[0022] The preferred sublingual dosage forms dissolve within a time period of at least about 2 minutes but less than about 10 minutes. More preferably, the dissolution time in water for the presently contemplated dosage forms is about 3 minutes to about 5 minutes.

[0023] The present invention is illustrated further by the following studies which were focused on two specific objectives. The first was to determine whether, relative to placebo response, patients who presented with "psychogenic" impotence (i.e., patients who were still capable of achieving erections) demonstrated improved erectile function and/or enhanced sexual desire post-dosing with sublingual apomorphine (APO). The second objective was to determine what dose(s) of various forms of sublingual APO are effective in this group of patients for inducing an erection that is sufficient for vaginal penetration.

[0024] Participating patients were selected from among those that initially presented with the complaint of impotence. These patients underwent a thorough urological assessment by a urologist as well as an assessment by a psychiatrist. Diagnostic testing for erectile difficulties was extensive and included the following: biochemical profile, nocturnal penile tumescence (NPT) monitoring, doppler flow studies, biothesiometry, corporal calibration testing with an intracorporal injection of triple therapy and dynamic cavernosometry. These tests were used to rule out any arterial, venous or peripheral neural causality of impotence. Any patients with abnormalities in any of these three areas were excluded from entry to the trials. The inclusion/exclusion criteria for all four pilot studies are set forth in Table V, below. Patients who met all criteria were diagnosed as having impotence primarily of a psychogenic origin. If there were no known medical contraindications to the use of a dopaminergic medication they were offered entry into an APO trial.

[0025] Instructions were given regarding the protocol by the research clinician, and an informed consent was obtained. Patients were advised that they were free to withdraw from the trial at any time without penalty or prejudice. They were tested on at least three separate days at three separate doses (placebo and two active medication doses) with an interval of no less than three days between. The experimental scheme described below was used in all four pilot studies.

[0026] Patients were seated in a comfortable chair and a RIGISCAN™ ambulatory tumescence monitor (Dacomed Corp., Minneapolis, Minnesota) was placed on the patient and the computer was set in the real time monitoring mode.

Blood pressure and heart rate were recorded pre-dosing with APO or placebo and at the end of the testing session. Visual analogue scales (VAS) were completed by the patient pre-dosing as well as post-dosing (at the end of the testing session). These scales reflected the patient's sense of well being, level of sedation, tranquilization, anxiousness, arousal and any changes in yawning behavior. In a single-blind fashion, apomorphine or placebo was administered to the patient sublingually. Doses of active medication varied on the formulation of the apomorphine administered (liquid or tablet). Because of the possibility of nausea and the tolerance to this effect that prior dosing conveys, the patient was given increasing doses at each testing. However, the patient was unaware of the dose that he was receiving (single-blind). Patients were instructed not to swallow the medication, but to keep it under their tongue and allow it to be absorbed there.

[0027] Symptoms as they were volunteered were recorded by the research clinician. If the patient complained of nausea or felt unwell in any way he was asked if he wanted to abort the trial. If the trial was aborted, the patient was given Gravol 50 mg. p.o. at that time. The patient was monitored by the research clinician until these side-effects had subsided. He was asked to return the following week for retesting at the same dose and was instructed to begin treatment with Domperidone 10 m.g. p.o. TID the day before and morning of his next session.

[0028] Patients not experiencing nausea or any other significant adverse effects within fifteen minutes post-dosing with APO or placebo viewed segments of standardized erotic videos to provide sexual stimulation. The following sequence of videos was viewed: a ten minute erotic video, a neutral video lasting between five and ten minutes in duration and finally another ten minute erotic video. The duration of the testing session for each dose level lasted between 45 and 60 minutes. After determining the most effective dose of apomorphine for the patient, he was then offered APO for domestic trial at that dose.

Results of Pilot Studies 1 to 4

[0029] The frequency and the magnitude of erectile responses were documented with each dose of apomorphine or placebo. Data obtained from the RIGISCAN™ monitor was downloaded and each session was scanned. Erection responses were then scored for rigidity (%) and tumescence (cm.) at both the tip and base of the penis and an overall score was given that corresponded to these parameters during the viewing of both erotic and neutral video segments (see Table VI, below). A score of less than 16 indicated erectile dysfunction and a poor response to apomorphine at that dose.

[0030] Visual analogue scales (See Table IX) were compared both pre- and post-dosing, and examined for changes in feeling of well being, levels of arousal, anxiousness, sedation/tranquilization and yawning behavior. Blood pressure and heart rate were also compared pre- and post-dosing.

[0031] Effects of apomorphine that were both reported to and observed by the research clinician were grouped into two categories: Adverse Effects (i.e., flushing, diaphoresis, nausea, vomiting, changes in blood pressure or heart rate) or Primary Effects (i.e., yawning and erections).

[0032] Each pilot study was reviewed under the categories mentioned above.

Pilot Study #1

[0033] The initial formulation evaluated was liquid apomorphine administered via sublingual route. APO was prepared by a clinic pharmacist and dissolved in a solution of sodium metabisulfite and ethylenediamine tetraacetic acid (EDTA). The final concentration was 100 mg./ml. Patients were tested on three separate occasions at three separate doses (placebo; 10 mg.; 20 mg.)

[0034] Twelve patients entered into this trial. All patients had reported erectile dysfunction greater than 1 year in duration. The age range in this group was from 38 to 60 years. One patient withdrew after placebo and another withdrew after adverse effects at the 20 mg. dose. That left a total evaluable group of ten. All ten patients had previously received yohimbine HCl for erectile dysfunction. Eight had failed a trial of yohimbine HCl. Of this group of eight, 6 were successful with apomorphine.

[0035] Seven (70%) were success (score of no less than 16 on both neutral and erotic video segments; Table VI) and three (30%) were categorized as failures with apomorphine. Six out of the seven successful patients continued on with a domestic trial of apomorphine at the dose that gave them the best response during testing. Three required treatment with Domperidone the day before and morning of apomorphine usage. The range of domestic use varied from two to seven months.

[0036] Analysis of visual analogue scales pre- and post-dosing with apomorphine indicated the following. At the end of the session patients were relaxed but not sedated. There was no evidence of arousal or anxiousness. Yawning behavior changes were evident on these scales with the incidence of yawning increasing between 15 and fifty minutes post-dosing and with each increase in dosing. Each patient experienced between two to five yawns per session. These changes were not evident with placebo.

[0037] The primary effect of yawning was both reported by patients and observed at both 10 mg. and 20 mg. doses. No yawning was reported with placebo. Adverse effects were reported at both dose levels. Two patients who did not experience nausea or diaphoresis were researched for similarities in their patient profiles but none were found. Anywhere from ten to fifteen minutes post-dosing the other eight patients developed sudden onset of various levels of nausea (and in one instance vomiting), diaphoresis, dizziness, double or blurred vision, decrease in both blood pressure and heart rate and pale or ashen coloring. Side effects varied from being transient and brief to lasting as long as from 30 to 40 minutes. One patient reported a stuffy nose starting approximately 30 minutes post-dosing and lasting for approximately 10 minutes. No adverse effects were reported post placebo dosing.

[0038] The foregoing Pilot Study leads to the following conclusions:

1. Apomorphine is effective in inducing erectile episodes without increasing libido in the "psychogenically" impotent male.
2. Both 10 mg. and 20 mg. doses produce erectile responses.
3. Both doses produced adverse effects (nausea, vomiting, diaphoresis, etc.) that would be unacceptable to patients and their partners, however. These effects can be counteracted with the use of Domperidone.

Pilot Study #2

[0039] The first sublingual tablet formulations evaluated were 2.5 and 5 mg. Patients were tested on three separate occasions at three separate doses (placebo; 2.5 mg., 5 mg.).

[0040] A total of eight patients entered into this trial. All patients reported erectile difficulties for more that two years. The age range was from 38 to 62 years. All had failed a trial of yohimbine HCl. One patient withdrew from the trial after experiencing adverse effects at the 5 mg. dose. That left a total of seven evaluable patients.

[0041] Two (29%) were successes (score of no less than 16; Table VI) and five (71%) were failures during lab testing. The two successful patients went onto a domestic trial of apomorphine at the 2.5 mg. dose which was the most effective and did not produce adverse effects. Both patients used apomorphine at home for no less than two months with satisfactory results.

[0042] Analysis of visual analogue scales pre- and post-dosing with apomorphine indicated the same trends as with the liquid apomorphine preparation. Patients were relaxed but not sedated. No evidence of arousal or anxiousness was noted..

[0043] The primary effect of yawning was both reported by patients and observed at both 2.5 mg. and 5 mg. doses. The incidence of yawning increased between fifteen and forty minutes post-dosing. At the 2.5 mg. dose all patients who failed testing had only one or two yawns per session. The 5 mg. dose not only produced adverse effects (nausea, diaphoresis, dizziness, blurred vision, facial flushing, drop in both heart rate and blood pressure) but also increased yawning responses to three to five times per session. The two successful patients experienced three to five yawns at both the 2.5 mg. and 5 mg. doses. These changes were not evident with placebo.

[0044] At the end of Pilot Study #2 the following conclusions were made:

1. There appears to be a correlation between the effectiveness of the dose and yawning response (poor responders experience less yawning).
2. Both 2.5 and 5 mg. doses produced erectile responses in some patients. The apparent 28% success rate was because of lab use only (failures were not given drug to take home) and lack of available intermediate doses.
3. In some instances the 5 mg. dose can produce adverse effects (i.e., nausea, diaphoresis, etc.) that may be unacceptable to patients and their partners. These effects can be counteracted with the administration of Domperidone or nicotine (e.g., by smoking).
4. The sublingual tablets were easy to administer and dissolved within five minutes.

Pilot Study #3

[0045] Apomorphine was evaluated as an aqueous intranasal spray (1.25 mg. per puff). The first patient was an anxious, 53 year old male who had been experiencing erectile dysfunction for two years. This patient had previously failed a trial of yohimbine.

[0046] He was tested on three separate occasions at three separate doses (placebo, 2.5 mg.; 3.75 mg.) and was categorized as a failure with the score of less than sixteen on both erotic and neutral video segments. He experienced yawning with both 2.5 mg. and the 3.75 mg. and was successful with this trial for two months until he inadvertently increased the dose. Adverse effects occurred within five minutes post-dosing (nausea and vomiting, dizziness, double and blurred vision, diaphoresis, and ashen coloring). The patient refused to rehy medication after this incident. He stated he did not like this formulation.

[0047] Patient No. 2 was twenty-one year old male with erectile problems of a duration of three years. He had failed a previous course of yohimbine HCl. Ten minutes post-dosing with apomorphine at 2.5 mg. he experienced yawing for a total of five yawns, and then experienced immediately major hemodynamic adverse effects. These included pale and ashen coloring, diaphoresis, nausea and vomiting, blurred vision, hypotension with a blood pressure of 70/50. Twenty minutes post adverse effect, vital signs were stable. The patient was feeling well, and coloring was good. This patient was then dropped from further testing.

[0048] Although the intranasal administration was effective in eliciting an erection, further testing of this intranasal formulation of apomorphine was discontinued because of possible overdose and increased side effects The foregoing experience illustrates the need for reliable and relatively safer dosage forms, however.

Pilot Study #4

[0049] New sublingual tablet formulations of apomorphine at 3, 4 and 5 mg. doses (Table I, above) were evaluated. Patients were tested on at least three separate occasions on at least three separate doses (placebo; 3 mg.; and 4 mg.). A 5 mg. sublingual dose was also tested in some patients. The results of this study are summarized in Tables VII and VIII A-C, below.

[0050] To date, twelve patients have been completely evaluated on this formulation. All patients reported erectile dysfunction for more than two years. The patients' age range was thirty-nine to sixty-six years. Three patients had been successful with yohimbine HCl in the past, and two had previously not tried this compound. Seven patients of this group of twelve had previously failed a trial of yohimbine HCl. Of this latter group of seven, four were successfully treated with apomorphine.

[0051] Eight (67%) have been successful with apomorphine to date. Four (33%) were failures with apomorphine. Both 3 mg. and 4 mg. doses produced erectile responses. Several patients went on to a trial of the 5 mg. sublingual dose which did not appear to be more effective than the relatively lesser doses in terms of erectile response. All eight of the successful patients continued on with the domestic use for a time period of one to four months. All patients reported good erectile activity and no side effects.

[0052] Analysis of visual analogue scales, both pre- and post-dosing with apomorphine, again indicated that the patients were relaxed but not sedated, and did not have feelings of arousal or anxiousness post-dosing. The new formulations tested (3 mg.; 4 mg.; and 5 mg.) were devoid of adverse effects. The patients felt well post testing, and did not report or demonstrate any adverse effects that had traditionally been seen with the administration of previous apomorphine liquid and intranasal preparations (Pilot Studies No. 1 and No. 3). The primary effect of yawning was still reported and observed at all doses, but the number and frequency of yawns was small (one or two).

[0053] The foregoing pilot study shows that 3-mg., 4-mg. and 5-mg. apomorphine doses are effective in inducing penile erections, and also that there are no serious adverse effects with these preparations. Domestic use of these preparations was well accepted by patients and their partners. They were content with the convenience of dosing approximately fifteen minutes prior to sexual activity. All patients have stated that this was more acceptable than dealing with dosing on a routine basis.

TABLE V

	Inclusion/Exclusion Criteria INCLUSION CRITERIA:	
1.	Age 18-66 years.	
2.	NPT circumference increase of 1.5 cm or more on one night and >70% rigidity.	
3.	ICI circumference increase of 1.5 cm or more and >70% rigidity.	
EXCLUSION CRITERIA:		
1.	Currently severe or life threatening systemic disease.	
2.	Clinically significant ECG abnormalities.	
3.	Personal or first degree family history of epilepsy.	
4.	Abnormal:	Hepatic/renal function
		Hematology
5.	Low:	pre-trial testosterone
	Low or High:	LH
	High:	Prolactin
6.	Hypertension requiring treatment.	
7.	History of depression requiring treatment with antidepressants, ECT, or hospitalization.	
8.	Symptomatic ischemic heart disease/or MI within the last three months.	
9.	Diabetes.	
10.	Failure to obtain informed consent.	
11.	Legal cases.	
12.	Unable or unwilling to comply with protocol.	
13.	Drinks more than (on average) 45 units alcohol per week/or uses illicit drugs.	
14.	History of syncope.	
15.	Prohibited Drugs: sympathetic or parasympathetic types drugs, Beta blockers, Vasodilators, psychotropic medications, tranquilizers, thiazides, Captopril, Verapmil, Furosemide, Spironolactone, Metochlopramide, Cimetidine or other drugs which are likely to influence erectile function.	

TABLE VI

Response to Erotic Videotape

1. Maximum increase in penile circumference

Circumference (cms.)		Score
0 - <0.5 cm.		0
0.5 - <1.0 cm.		1
1.0 - <1.5 cm.		2
1.5 - <2.0 cm.		3
2.0 - <2.5 cm.	lasts <1 min.	4
2.5 or more	lasts <1 min.	5
2.0 - <2.5 cm.	lasts at least 1 min.	6
2.5 or more	lasts at least 1 min.	7
3.0 or more	lasts at least 5 min.	8
3.0 or more	lasts at least 10 min.	9

	Score
A. Maximum increase in penile tip circumference	____
B. Maximum increase in penile basal circumference	____

2. Maximum penile rigidity

Rigidity (%)	Score
0 - <10	0
10 - <20	1
20 - <30	2
30 - <40	3
40 - <50	4
50 - <60	5
60 - <70	6
70 - <80	7
80 - <90	8
90 - 100	9

	Score
C. Maximum penile tip rigidity	____
D. Maximum penile basal rigidity	____

3. Total score (A, B, C & D) ____ ____

A score of less than 16 indicates erectile dysfunction

TABLE VII

Summary of Results from Pilot Study #4 in Psychogenic Patients

	PLACEBO		Apomorphine • HCl Sublingual Tablet									
			3 Mg Dose (μg/kg)		4 Mg Dose (μg/kg)			5 Mg Dose (μg/kg)				
Patient # (Wt., kg)	Erotic #1	Neutral #1	Erotic #2	Neutral #2	Erotic #3	Neutral #3	Erotic #4	Neutral #4
401 (68.5)	31	28	29 (44)	27 (44)	33 (58)	27 (58)		
402 (70.3)	12	4	12 (43)	4 (43)	17 (57)	6 (57)		
403 (118)	16	4	22* (25)	5 (25)	22* (34)	25 (34)		
404 (83.5)	24	10	26* (36)	17 (36)	25* (48)	17 (48)		
405 (78)	11	1	18* (38)	6 (38)	12 (51)	8 (51)	10 (64)	5 (64)
406 (80)	14	5	18* (38)	17 (38)	17* (50)	2 (50)		
407 (100)	8	0	18* (30)	4 (30)	10 (40)	3 (40)		
408 (86.2)	28	18	32 (35)	21 (35)	34 (46)	22 (46)		
409 (93)	2	0	4 (32)	1 (32)	8 (43)	6 (43)	5 (54)	4 (54)
410 (80)	3	0	13 (38)	16 (38)	8 (50)	7 (50)		
411 (98)	13	5	26* (31)	23* (31)	24* (42)	20 (42)		
412 (73)	7	3	7 (41)	1 (41)	28* (55)	19* (55)		

* Patients with score higher than 16 (see scoring table) are positive respondents.

Out of 12 patients who were treated in this study, 5 showed improvement at both 3 mg and 4 mg doses. Two (2) showed response only at one dose.

No improvement in clinical response was observed at 5 mg dose.

[0054] The data of Pilot Study #4 were analyzed in two ways. First, mean erectile function was compared across placebo, 3 mg and 4 mg doses under two stimulus backgrounds, erotic and neutral. Next erectile function scores were dichotomized, with values less than sixteen considered to reflect erectile insufficiency.

A. Mean Erectile Function

[0055] Table VIII A shows means and standard errors for all three treatments under both backgrounds, erotic and neutral. Means were compared using a restricted maximum likelihood generalized linear model containing two main effects, treatment and stimulus, and the treatment by stimulus interaction. An appropriate variance-covariance structure was established for the underlying statistical model using Akaike's criterion. Table VIII B presents the statistical results for the main effects of treatment and of stimulus, for the treatment by stimulus interaction, and for orthogonal contrasts within the erotic and neutral conditions. It can be seen that the treatment main effect (i.e., general difference across treatment conditions without regard to stimulus background) is statistically significant; that the main effect of stimulus (i.e., general difference across stimulus backgrounds without regard to treatment) is statistically significant; and that the treatment by stimulus interaction is not statistically significant. These findings imply that active treatment is more effective than placebo and that this finding, although stronger when using an erotic stimulus, is true regardless of stimulus background (see FIGURE 1). The orthogonal (statistically independent) contrasts confirm that active treatment is superior at a statistically significant level under both erotic and neutral conditions, but also indicate that the difference between the 3 mg and 4 mg dose does not exceed that expected by chance for the number of patients (12) used in this study.

B. Percent Successful Erectile Function

[0056] FIGURE 2 and Table VIII C show that the statistically significant superiority of active over placebo treatment, regardless of stimulus background, is maintained when the erectile function scores are classified to reflect success (score at least 16) or failure (score less than 16).

TABLE VIII A

Mean and Percent Successful Erectile Function				
Stimulus	**Treatment**	**N**	**Mean (SE)**	**Percent (SE)**
Erotic	Placebo	12	14.08 (2.69)	33.33 (13.61)
	3 mg	12	18.75 (2.51)	66.67 (13.61)
	4 mg	12	19.83 (2.67)	66.67 (13.61)
Neutral	Placebo	12	6.50 (2.45)	16.67 (10.76)
	3 mg	12	11.83 (2.68)	50.00 (14.43)
	4 mg	12	13.50 (2.61)	50.00 (14.43)
Note: Mean (SE) from SAS PROC UNIVARIATE. Percent (SE) from SAS PROC CATMOD.				

TABLE VIII B

Anova for Mean Erectile Function				
EFFECT		**DF**	**F**	**P-value**
Treatment		2,66	11.56	0.0000
Stimulus		1,66	37.14	0.0000
Treatment by Stimulus		2,66	0.10	0.9046
Contrasts				
Erotic:	Placebo vs. Treatment	1,66	9.30	0.0033
Erotic:	3 mg vs. 4 mg	1,66	0.30	0.5849
Neutral:	Placebo vs. Treatment	1,66	13.03	0.0006
Neutral:	3 mg vs. 4 mg	1,66	0.71	0.4014
Note: Restricted maximum likelihood analysis performed using SAS PROC MIXED.				

TABLE VIII C

Logistic Regression for Percent Successful Erectile Function				
EFFECT		**DF**	**X^2**	**P-value**
Treatment		2	15.36	0.0005
Stimulus		1	5.14	0.0233
Treatment by Stimulus		2	0.00	1.0000
Contrasts				
Erotic:	Placebo vs. Treatment	1	9.60	0.0019
Erotic:	3 mg vs. 4 mg	1	0.00	1.0000
Neutral:	Placebo vs. Treatment	1	9.60	0.0019
Neutral:	3 mg vs. 4 mg	1	0.00	1.0000
Note: Analysis performed using SAS PROC CATMOD.				

TABLE IX

Visual Analogue Scale (VAS) (to be completed by the patient)				
Please mark each line clearly at the point which indicates how you are feeling right now. Each line represents the full range of each feeling. (There are no right or wrong answers)				
				Score (mm)
1.	Alert	_____	Drowsy	____
2.	Calm	_____	Excited	____
3.	Yawning	_____	Not Yawning	____
4.	Fuzzy	_____	Clear Headed	____

TABLE IX (continued)

Visual Analogue Scale (VAS) (to be completed by the patient)				
Please mark each line clearly at the point which indicates how you are feeling right now. Each line represents the full range of each feeling. (There are no right or wrong answers)				
				Score (mm)
5.	Well Coordinated	_____	Clumsy	____
6.	Tired	_____	Energetic	____
7.	Contented	_____	Disconnected	____
8.	Troubled	_____	Tranquil	____
9.	Mentally slow	_____	Quick Witted	____
10.	Tense	_____	Relaxed	____
11.	Attentive	_____	Dreamy	____
12.	Stomach Upset	_____	Feeling Well	____
13.	Anxious	_____	Carefree	____
(measure from left to right)				

Dose Evaluation Study

[0057] Clinical response to sublingual administration of apomorphine was evaluated utilizing a group of 60 non-vasculogenic impotent patients. Each patient had a history of erectile dysfunction for at least 3 months, normal biothesiometry response, and normal cavernosometry results.

[0058] The patients were divided into seven groups. Each group received a predetermined dosage of apomorphine for 20 days in the form of apomorphine hydrochloride tablets 20 minutes prior to intercourse. Seven different dosages were evaluated - 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg and 10 mg. The tablet constituents were those shown in Table I, above. Assessment of response was made on the basis of the patient's report of his experience. A response was deemed positive when the patient experienced an erection sufficiently rigid to effect penetration. Side effects such as nausea and/or vomiting, if present, were noted as well.

[0059] The results of this study are compiled in Table X, below.

TABLE X

Results of Dose Evaluation Study							
No. of Patients	Dosage, mg	Positive Responses		Nausea		Vomiting	
		No.	%	No.	%	No.	%
5	3	0	0	0	0	0	0
5	4	2	40	1	20	1	20
10	5	5	50	2	20	1	10
10	6	7	70	2	20	2	20
10	7	7	70	2	20	2	20
10	8	7	70	3	30	3	30
10	10	8	80	4	40	4	40

[0060] From the foregoing Table it can be seen that at a 4-mg dosage 40 percent of patients had a positive response, at a 5-mg dosage 50 percent of patients had a positive response, at 6-mg, 7-mg, and 8-mg dosages 70 percent of patients had a positive response and at a 10-mg dosage 80 percent of patients had a positive response. However, the incidence of side effects increased as well as the dosage was increased.

[0061] The aforesaid apomorphine dosage forms are also well suited for diagnosing male human patients suffering

from male erectile dysfunction. For diagnostic purposes, at least about 3 milligrams of apomorphine are administered sublingually to the patient and the patient is exposed to a visual erotic stimulus, e.g., an erotic videotape, while the patient's response thereto is monitored. If deemed desirable for diagnostic purposes, up to about 10 milligrams of apomorphine can be administered to the patient.

[0062] In particular, the patient's maximum increase in penile circumference (preferably tip as well as basal) is determined and the patient's maximum penile rigidity (preferably tip as well as basal) is determined. The determined circumferential increase and rigidity values are then compared against a predetermined base value. Equivalent methods of determining tumescence and rigidity can also be utilized.

[0063] The foregoing discussion and the reported studies are intended as illustrative of the present invention.

Claims

1. The use of apomorphine or a pharmaceutically-acceptable acid addition salt thereof for the manufacture of a sublingual pharmaceutical dosage form containing apomorphine or its add addition salt in a sufficient amount for treating functional impotence of male patients without causing nausea.

2. Use as claimed in claim 1 wherein the amount of apomorphine or its acid addition salt in the dosage form is in the range from 25 to 60 micrograms per kilogram of patient body weight.

3. Use as claimed in claim 1 wherein the dosage form contains 2 to 10 mg apomorphine or its acid addition salt.

4. The use of apomorphine or a pharmaceutically-acceptable acid addition salt thereof for the manufacture of a sublingual pharmaceutical dosage form containing apomorphine or its acid addition salt in an amount of at least 2.5 mg for diagnosing functional impotence of male patients.

5. Use as claimed in any one of claims 1 to 4 wherein the acid addition salt is apomorphine hydrochloride.

6. Use as claimed in any one of claims 1 to 5 wherein the dosage form includes β-cyclodextrin or a β-cyclodextrin derivative

7. Use as claimed in claim 6 wherein the β-cyclodextrin derivative is hydroxypropyl-β-cyclodextrin.

8. Use as claimed in any one of claims 1 to 7 wherein the dosage form includes mannitol and ascorbic acid.

9. A sublingual apomorphine dosage form comprising 2 to 10 milligrams of apomorphine or its pharmaceutically-acceptable acid addition salt, β-cyclodextrin or a β-cyclodextrin derivative.

10. The dosage form as claimed in claim 9, wherein the β-cyclodextrin derivative is hydroxypropyl-β-cyclodextrin.

11. The dosage form as claimed in claim 9 or 10 which additionally comprises mannitol and ascorbic acid.

Patentansprüche

1. Die Verwendung von Apomorphin oder seines pharmazeutisch verträglichen Salzes mit einer Säure zur Herstellung einer sublingualen pharmazeutischen Dosierungsform, die Apomorphin oder sein Salz in einer ausreichenden Menge enthält, um funktionelle Impotenz bei männlichen Patienten zu behandeln, ohne Übelkeit hervorzurufen.

2. Verwendung nach Anspruch 1, wobei die Menge an Apomorphin oder seinem Salz in der Dosierungsform im Bereich zwischen 25 und 60 Mikrogramm pro Kilogramm Körpergewicht des Patienten liegt.

3. Verwendung nach Anspruch 1, wobei die Dosierungsform 2 bis 10 Milligramm Apomorphin oder seines Salzes enthält.

4. Verwendung von Apomorphin oder seines pharmazeutisch verträglichen Salzes mit einer Säure zur Herstellung einer sublingualen pharmazeutischen Dosierungsform, die Apomorphin oder sein Salz in einer Menge von mindestens 2,5 mg enthält, zur Diagnose von funktioneller Impotenz bei männlichen Patienten.

5. Verwendung nach einem der Ansprüche 1 bis 4, wobei das Salz Apomorphin-Hydrochlorid ist.

6. Verwendung nach einem der Ansprüche 1 bis 5, wobei die Dosierungsform β-Cyclodextrin oder ein β-Cyclodextrinderivat einschließt.

7. Verwendung nach Anspruch 6, wobei das β-Cyclodextrinderivat Hydroxypropyl-β-cyclodextrin ist.

8. Verwendung nach einem der Ansprüche 1 bis 7, wobei die Dosierungsform Mannit und Ascorbinsäure einschließt.

9. Sublinguale Apomorphin-Dosierungsform, umfassend 2 bis 10 Milligramm Apomorphin oder seines pharmazeutisch verträglichen Salzes mit einer Säure, β-Cyclodextrin oder ein β-Cyclodextrinderivat.

10. Dosierungsform nach Anspruch 9, wobei das β-Cyclodextrinderivat Hydroxypropyl-β-cyclodextrin ist.

11. Dosierungsform nach Anspruch 9 oder 10, umfassend zusätzlich Mannit und Ascorbinsäure.

Revendications

1. Utilisation d'apomorphine ou d'un sel d'addition d'acide pharmaceutiquement acceptable de celle-ci pour la production d'une forme galénique pharmaceutique sublinguale contenant de l'apomorphine ou son sel d'addition d'acide en une quantité suffisante pour le traitement de l'impuissance fonctionnelle de patients mâles sans provoquer de nausées.

2. Utilisation selon la revendication 1, dans laquelle la quantité d'apomorphine ou de son sel d'addition d'acide dans la forme galénique est dans l'intervalle de 25 à 60 microgrammes par kilogramme de poids corporel du patient.

3. Utilisation selon la revendication 1, dans laquelle la forme galénique contient de 2 à 10 mg d'apomorphine ou de son sel d'addition d'acide.

4. Utilisation d'apomorphine ou d'un sel d'addition d'acide pharmaceutiquemnent acceptable de celle-ci pour la préparation d'une forme galénique pharmaceutique sublinguale contenant l'apomorphine ou son sel d'addition d'acide en une quantité d'au moins 2,5 mg pour le diagnostic de l'impuissance fonctionnelle de patients mâles.

5. Utilisation selon l'une quelconque des revendications 1 à 4, dans laquelle le sel d'addition d'acide est du chlorhydrate d'apomorphine.

6. Utilisation selon l'une quelconque des revendications 1 à 5, dans laquelle la forme galénique comprend de la β-cyclodextrine ou un dérivé de β-cyclodextrine.

7. Utilisation selon la revendication 6, dans laquelle le dérivé de β-cyclodextrine est de l'hydroxypropyl-β-cyclodextrine.

8. Utilisation selon l'une quelconque des revendications 1 à 7, dans laquelle la forme galénique comprend du mannitol et de l'acide ascorbique.

9. Forme galénique d'apomorphine sublinguale comprenant 2 à 10 milligrammes d'apomorphine ou de son sel d'addition d'acide pharmaceutiquement acceptable, de la β-cyclodextrine ou un dérivé de β-cyclodextrine.

10. Forme galénique selon la revendication 9, dans laquelle le dérivé de β-cyclodextrine est de l'hydroxypropyl-β-cyclodextrine.

11. Forme galénique selon la revendication 9 ou 10, qui comprend en outre du mannitol et de l'acide ascorbique.

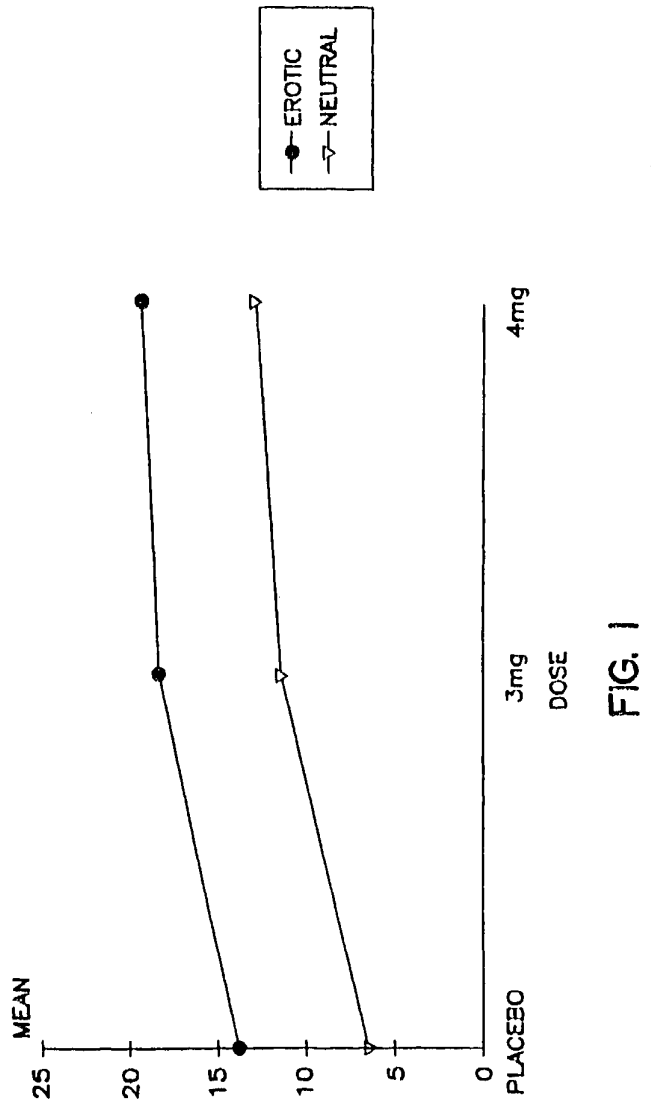


FIG. 1

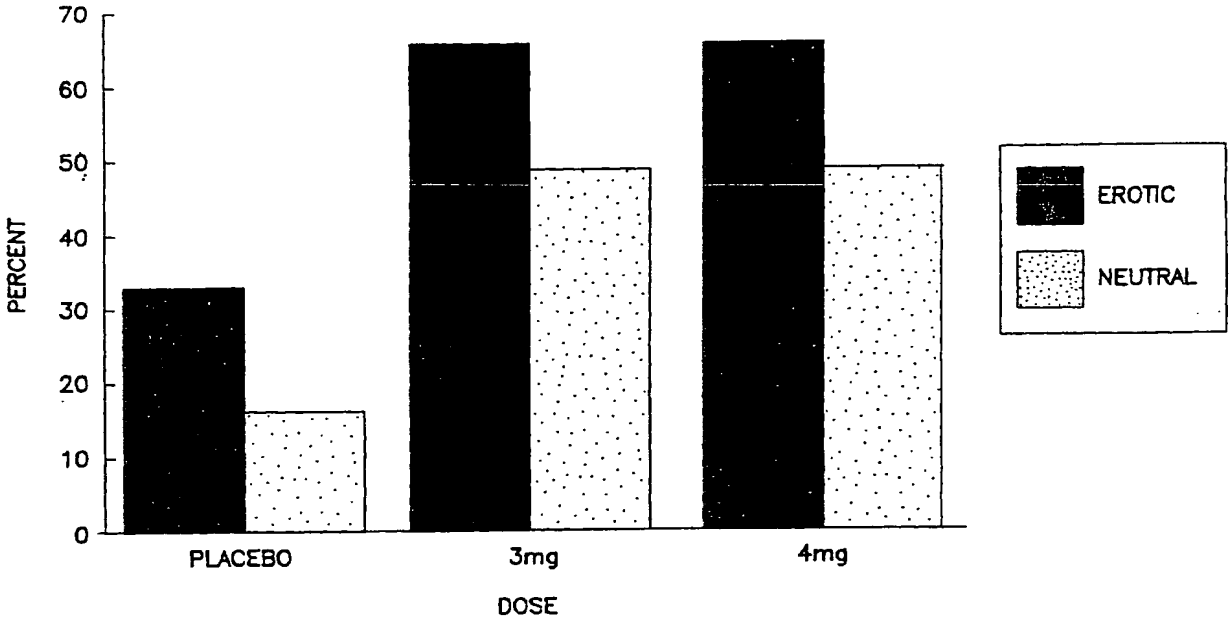


FIG. 2

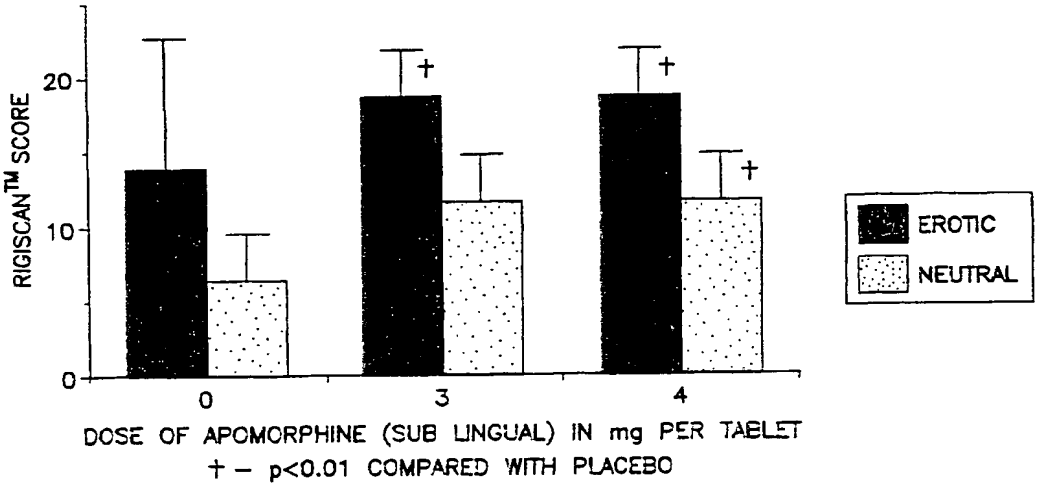


FIG. 3